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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,140	10/31/2005	Eva Kontsekova	SONN:065US	5448

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EXAMINER	
EPPS SMITH, JANET L	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,140	KONTSEKOVA, EVA	
	Examiner	Art Unit	
	Janet L. Epps-Smith	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-42* is/are pending in the application.

4a) Of the above claim(s) *35-38,41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-08-09, 3-28-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

ETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/08/2009 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 33-42 are presently pending.

Response to Arguments

Election/Restriction

4. Although the restriction requirement was made ***final*** in the prior Office Action, Applicants continued to traverse the examiner's position. However, Applicants continue to argue that the type IA tau molecule set forth in the instant claim 24 is not disclosed in the prior art, and therefore the holding of lack of unity of invention is improper. According to Applicants, the examiner has inaccurately characterized the teachings of the specification. In this regard, Applicant's arguments are not appropriate since the invention at hand is described by the claims, and it is inappropriate for Applicants to require the examiner to limit the scope of the claims to limitations recited in the claims. Moreover, contrary to Applicant's assertions, "[U]SPTO personnel are to give claims

their broadest reasonable interpretation in light of the supporting disclosure. In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). *Limitations appearing in the specification but not recited in the claim should not be read into the claim*. E-Pass Techs., Inc. v. 3Com Corp., 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) (claims must be interpreted "in view of the specification" without importing limitations from the specification into the claims unnecessarily)."

5. Again, contrary to Applicant's assertions, the instant claims do not recite any particular conformation, the only structural information recited in the claims is that defined by the sequences recited in the claims. Although, there is a discussion of the sequence of SEQ ID NO: 1 described in WO96/30766 in the specification as filed. The sequence of type I tau of the instant Application is identical to that of the prior art. Therefore, absent evidence to the contrary, there is nothing recited in the claims, for example some form of differential post translational modification, that would suggest that the SEQ ID NO: 1 recited in the claims is structurally any different from the type I tau of SEQ ID NO: 1 described in WO 96/30766. Applicants assert that the tau polypeptides described by Novak et al. (1993) "do not have biological structural pathological properties common with 'real world' tau proteins, especially tau proteins being connected with Alzheimer's disease." First it is noted that these "*biological structural pathological properties*" are not even clearly defined, therefore it is unclear what Applicants are attempting to base their arguments upon.

6. Moreover, to further justify the lack of unity of invention previously set forth, it is noted that the instant claims, and those claims as originally filed were drawn to multiple

non-human transgenic animals, specifically wherein the transgenic animal expresses (1) N- and C-terminally double truncated type IA tau molecule; (2) type IB tau molecule; (3) type IIA molecule; or (4) type IIB tau molecule; and methods comprising the use of one of said transgenic animals of (1)-(4) for screening or testing a candidate compound for utility in the treatment of Alzheimer's disease. As per 37 CFR § 1.475(b)-(d): "[A]n international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or
(2) A product and process of use of said product; or
(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or
(4) A process and an apparatus or means specifically designed for carrying out the said process; or
(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

(c) If an application contains claims to more or less than one of the combinations of categories of invention set forth in paragraph (b) of this section, unity of invention might not be present.

(d) If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and §1.476(c)."

7. Therefore, in the instant case, as per CFR § 1.475(d), since the instant claims are drawn to multiple categories of invention, i.e. the claims recite multiple patentably distinct products and methods, the instant claims are considered to lack unity of invention. Therefore, Applicant's arguments are not sufficient to overcome the previous

holding of lack of unity of invention. As stated in the prior Office Action, the restriction requirement mailed 4/11/2007 remains final.

8. Since the prior Restriction/Election (Lack of Unity of Invention) requirement was made final, and it is noted that in the reply filed 6/11/2007 Applicants elected IIA tau with traverse, claims 39-40, which read on type IIA tau, will be joined with the elected invention.

9. Therefore, claims 33-34 and 39-40 are pending for examination, and claims 35-38 and 41-42 are withdrawn as being directed to a non-elected invention.

10. The requirement is still deemed proper and is therefore made FINAL.

11. Should Applicants continue to traverse the finality of this restriction, Applicants are requested to follow the guidelines set forth in 37 CFR§1.181, "[A]fter a final requirement for restriction, the applicant, in addition to making any reply due on the remainder of the action, may petition the Director to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested (see § 1.181)."

Claim Rejections - 35 USC § 112

12. Claims 33-34 remain rejected and claims 39-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a transgenic mouse and rat comprising a genome having a double truncated tau sequence integrated therein, does not reasonably provide enablement for making a transgenic animal of *any* species of animal, wherein the genome of said animal

comprises a double truncated tau sequence integrated into the endogenous tau equivalent gene of said any species of animal, and further wherein said animal exhibits Alzheimer's disease associated risk factors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

13. Applicant's arguments filed 9/08/09 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the grounds that the Examiner's interpretation of the experimental data presented in the Filipcik Declaration demonstrated that the "[g]eneration of transgenic animals with relevant phenotypes ***was*** not unpredictable." Contrary to Applicant's assertions the data presented in the Declaration was not presented in the specification as filed, and the constructs used to produce the phenotypes in the transgenic lines were not described in the specification as filed or in the Declaration. Therefore, contrary to Applicant's assertions the data presented in the Filipcik Declaration does not provide evidence of unpredictability associated with the generation of transgenic animals with a relevant phenotype.

14. Moreover, the showing set forth in the Filipcik Declaration is not commensurate in scope with the claims of the instant invention which read on a non-human transgenic animal of any species. Contrary to Applicant's assertions, although transgenic rats expressing a truncated tau protein were produced and which exhibit a neurofibrillary phenotype. There is no clear correlation between the production of a neurofibrillary phenotype in rat, and the production of any non-human transgenic animals (e.g., pig,

sheep, cattle, rabbit, rat, mink, monkey, and etc.), wherein said animals exhibit a neurofibrillary pathology producing activity as a model of Alzheimer's disease.

15. Moreover, Applicants provide a description of data set forth in the Koson et al. (2008) reference. However, again, Applicants do not describe the constructs used in this reference to produce the transgenic animals set forth in this reference. The constructs used in this reference were described in Zilka et al. (2006; see IDS 3-02-09, reference C50), and are described as follows:

"The transgene construct was prepared by ligation of a cDNA coding for human tau protein truncated at amino acid positions 151–391, into the mouse Thy-1 gene downstream of the brain promoter/enhancer sequence. The original Thy-1 gene sequence coding for exons II–IV, together with thymus enhancer sequence was replaced by the cDNA. Transgenic DNA was linearized by cleavage with EcoRI. Vector sequences were removed prior to microinjection." (see page 3582)

The transgenes used to produce the phenotypes produced in Koson et al. comprised the use of tissue specific enhancer sequences that allowed the expression of the truncated tau protein in the brain. The specification as filed does not teach such constructs, nor is there specific guidance in the specification as filed to design such a construct. Moreover, this reference does not teach that the doubly truncated tau proteins as set forth in the instant claims.

16. Applicants argue that the Examiner's argument that the expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter is unavailing since the claims do not recite a promoter and do not need to. According to Applicants, expression of a gene of interest in a transgenic animal is well known. Moreover, Applicants allege numerous promoters are known and ready available in the art to drive transgene expression in the central nervous system of various mammals including the CMV promoter, as such, it would only require routine cloning procedures

to place the cDNA molecule coding for N- and C-terminally truncated tau molecules under the control of the appropriate promoter. Applicant's arguments are not persuasive since Applicants have not provided sufficient guidance for how to make and use promoterless DNA constructs to efficiently express a gene of interest. Furthermore, Applicants do not provide an enabling disclosure for the use of any promoter resulting in efficient expression of the truncated tau protein in the rat CNS to exhibit the claimed phenotype such as the CMV promoter. As the CMV promoter, for example, is active in a wide range of tissues and drives high-level constitutive expression, it will generate a transgenic non-human animal exhibiting global expression of the truncated tau gene that will necessarily result in a different transgene phenotype.

17. Moreover, Applicants do not provide any specific information regarding the tissue specific promoters used in the experiments as set forth in the Filipcik Declaration, or the Koson et al. reference to provide specific expression of the doubly truncated tau proteins used to produce the rat transgenic lines having a neurofibrillary phenotype. Although, knowledge of tissue specific promoters was known in the art, it is noted that the instant claims do not even require the use of a tissue specific promoter to express the doubly truncated tau proteins of the instant invention. Therefore the scope of the claims encompasses the use of an undefined construct for the production of a transgenic non-human animal of any species, wherein said transgenic animal would be useful as a model for Alzheimer's disease. There is no guidance in the specification as filed in this regard. Again, there is generic teaching for the production of a transgenic animal. However, again the skilled artisan given the specification as a guide, and what

is known in the prior art, would have had to undertake undue experimentation to practice the full scope of the claimed invention.

18. Applicants argue that there is no recitation in the claims of amino acids that are substituted, deleted or inserted within the minimally truncated tau core. The examiner agrees that the claims do not recite this phrase. However, it is clear from the specification as filed that the truncated tau proteins encompass, for example in regards to the type IIA tau molecule, wherein:

19. "[0036] The present invention also provides N- and C-terminally double truncated tau molecules, which are characterized by the following features ("type IIA tau molecules"): [0037] the molecules have at least the first 68 N-terminal amino acids and at least the last 40 C-terminal amino acids of the 4 repeat containing tau43 or the first 68 N-terminal amino acids and at least the last 20 C-terminal amino acids of the 3 repeat containing tau44 truncated, [0038] the molecules are detectable in Alzheimer's diseased brain tissue, whereas the molecules are not detectable in normal healthy brain tissue, [0039] the molecules have a higher microtubule assembly promoting activity than wild type tau in an in vitro microtubule assembly assay, [0040] said microtubule assembly promoting activity can be eliminated by specific inhibitory, neutralising monoclonal antibodies against said molecules in a microtubule assembly assay and [0041] the pathologic activity of said molecules relies their binding to the microtubular network defined by the microtubule polymerisation promoting activity."

20. However, the scope of claim 33, for example, is not limited to any particular amino acid sequence structure or species for the N-, C-terminally double truncated tau

proteins recited in the claims, therefore the overall structure of tau proteins recited in these claims encompass any allelic or polymorphic variant form of these proteins. As stated in the prior Office Acton, though the recombinant technology for the generation of new mutant proteins is highly developed, the ability to determine *a priori* whether a mutation and/or deletion and/or insertion will generate a functional protein is not predictable. Since the relationship between a sequence of a peptide and its tertiary structure is not well understood and is not predictable, it would require undue experimentation for one skilled in the art to determine alternative sequences of N- and C-terminally truncated tau protein molecules, such that transgenic animal expressing this truncated protein would produce an animal model suitable for isolating therapeutic candidates for the treatment of Alzheimer's disease.

21. Moreover, although Applicants make reference to a variety of publications as evidence that a variety of animals are capable of exhibiting a neurofibrillary pathology, see the following:

Hartig et al. (European Journal of Neuroscience, Vol. 25, pp. 69-80, 2007),

Huang et al., (Brain Research 771, 1997, 213-220),

Gotz (Brain Research Reviews 35 (2001) 266-286), and

Lewis et al., (Nat Genet. 2000 Aug; 25(4):402-5).

22. Again, contrary to Applicant's assertions, due to the unpredictability of the art in using transgenic animals as models for Alzheimer's disease when there is not evidence of record, at the time the invention was made, to substantiate a reasonable correlation between any non-human transgenic animals (e.g., pig, sheep, cattle, rabbit, rat, mink,

monkey) exhibiting neurofibrillary pathology producing activity as a model of Alzheimer's disease. This unpredictability is due to the distinct phenotypes observed in closely related rodents such rats and mice in the expression of the same gene e.g., Amyloid Precursor Protein (APP; see Gotz et al. (2001)) and, conversely, the pleiotropic roles of the same gene e.g., the NF tangles associated with widely divergent neurodegenerative diseases in addition to Alzheimer's disease in terms of their pathologic mechanisms including supranuclear palsy, parkinsonism linked to chromosome 17, corticobasal degeneration, and others (Lewis et al. (2000)).

23. Due to the breadth of the claimed invention, the limited and prophetic guidance in the specification as filed, and the unpredictability associated with the production of a transgenic animal exhibiting a phenotype that correlates with risks factors associated with Alzheimer's disease, the skilled artisan would have to undertake undue experimentation to practice the full scope of the claimed invention.

Double Patenting

24. Claims 33-34 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17-21 of copending Application No. 10/521049. According to Applicants, a terminal disclaimer will be filed if the copending application issues as a US Patent. Also, Applicants stated that if the obvious type double patenting rejection remains as the only rejection of record, the examiner should withdraw the rejection.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/
Primary Examiner, Art Unit 1633